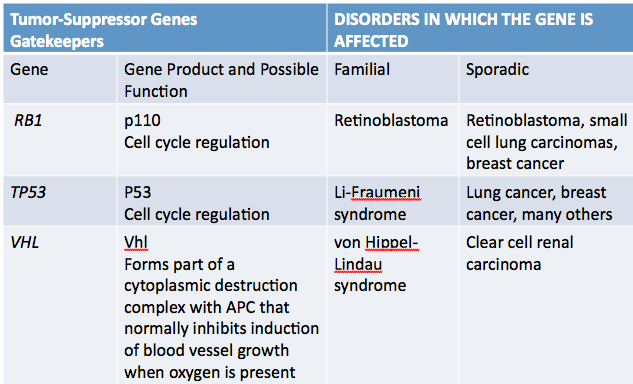
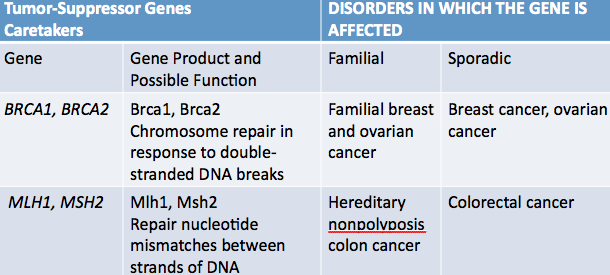
Cancer Genetics – Trumbly

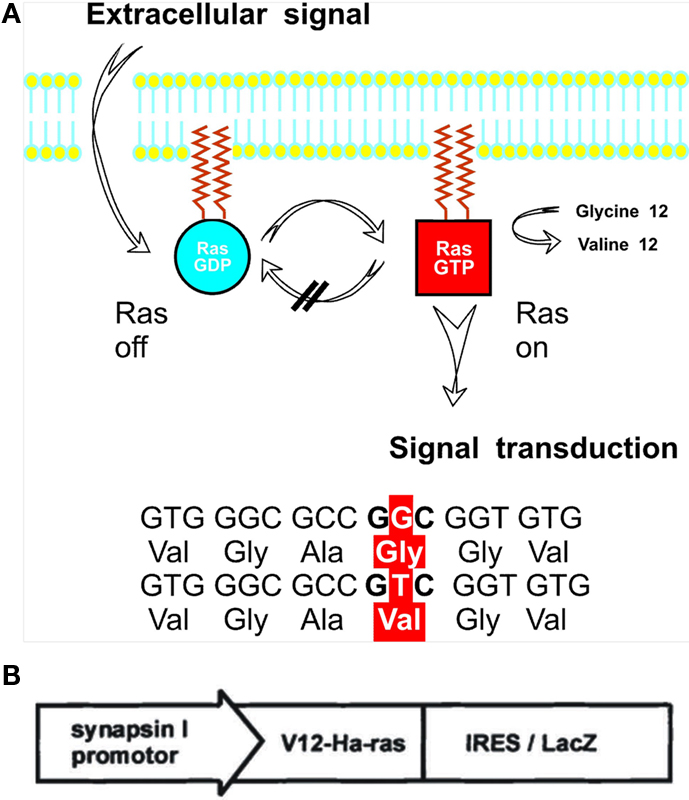
1. *Identify the tissue types affected by sarcomas, carcinomas, and hematopoietic and lymphoid tumors. (p. 832)*
   1. **Sarcomas** – tumor in mesenchymal tissue (bone, muscle, CT, nervous)
   2. **Carcinomas** – tumor in epithelial tissue (lining intestine, bronchi, mammary ducts)
   3. **Hematopoietic** – malignant neoplasms (leukemia and lymphoma) spread throughout bone marrow, lymphatic system and peripheral blood
2. *Describe the two major types of familial colon cancer, the genes affected, and the mechanisms leading to cancer formation. (p. 849)*
   1. **Familial Adenomatous Polyposis (FAP)** – 1% of cases, mutation in adenomatous polyposis coli gene (APC) 🡪 >95% get cancer if mutation present
      1. Normally B-catenin is bound to E-cadherin and floats around cell causing transcription (Myc) – APC w/ a serine-threonine kinase phosphorylates extra B-catenin and degrades, stopping from over-production of cells
      2. Mutated APC (no APC), B-catenin leads to unregulated growth
      3. APC gene is main mutation –FAP heterozygotes present with many polyps – must undergo colonectomy
   2. **Hereditary nonpolyposis colon cancer (HNPCC)** – 2-4% of cases - mutations in MSH2 and MLH1 genes (carry out mismatch repair of DNA) 🡪 60-80% get cancer
      1. Mutation in MSH2 and MLH1 🡪 mismatch repair genes (MMR)
      2. LOH at MMR gene 🡪 tumor formation
3. *Describe mechanisms responsible for converting proto-oncogenes to oncogenes, with the following as examples: Ras, receptor tyrosine kinases, Abl, Bcl2, and Myc. (p. 840)*
   1. Ras – point mutations (displayed in notes)
   2. Receptor tyrosine kinase – deletion mutations that remove regulatory domains – *Multiple endocrine adeomatosis* – Philadelphia chrom translocation (22🡪9 containing ABL oncogene)
   3. Abl – chromosomal translocations that produce novel fusion proteins – *Chronic myelogenous leukemia* – chrom (9🡪22) fuses BCR and ABL genes, encoding a protein with unregulated protein kinase activity (DRUG – GLEEVEC)
   4. Bcl2 – Chromosomal translocation to juxtapose a strong promoter upstream and the proto-oncogene such that it is inappropriately expressed – *follicular lymphoma*
   5. Myc – gene amplification resulting in overexpression – *her-2 breast cancer*
4. *List common cellular roles of proto-oncogenes. (p. 833)*
   1. **Oncogene** – mutant, activated, allele of a proto-oncogene (*normal* cellular protein coding gene that promotes growth and survival of cells) – oncogenes lead to malignancy by stimulating proliferation or inhibiting apoptosis
   2. **PROTO***-***ONCOGENES encode proteins that:**
      1. Proteins in signaling pathways for cell proliferation
      2. Transcription factors that control the expression of growth promoting genes
      3. Inhibit programmed cell death machinery
5. *State the difference between gatekeeper and caretaker tumor suppressor genes, and give examples of each. (p. 833)*
   1. **TUMOR SUPPRESSOR GENES (TSGs)**
   2. Gatekeeper TSGs – control cell growth 🡪 block tumor development by regulating the transition of cells through checkpoints in cell cycle
      1. Regulators of check points and mediators of programmed cell death
   3. Caretaker TSGs – protect integrity of the genome 🡪 loss of function/inhibition of caretaker genes permit mutations to accumulate in oncogenes and gatekeeper genes 🡪 therefore, initiating and promoting cancer
      1. They encode: proteins responsible for detecting and repairing mutations, proteins used in normal chromosome disjunction during mitosis, components of programmed cell death machinery
6. *List common cellular functions of tumor suppressor genes. (p. 842)*
   1. **Gatekeepers**
      1. **
   2. **Caretakers**
      1. ******
7. *Define the following terms: neoplasia, malignant tumor, benign tumor, sarcoma , carcinoma, tumor suppressor genes (TSGs), gatekeeper TSGs, caretaker TSGs, loss of heterozygosity (LOH).*
   1. **Neoplasia** – uncontrolled cellular proliferation leading to a mass/tumor (neoplasm)
   2. **Malignant tumor** – uncontrolled growth capable of metastasizing (spreading)
   3. **Benign tumor** – non invasive, growth arrested
   4. Tumor suppressor genes (TSGs)
      1. Gatekeeper TSGs
      2. Caretaker TSGs
   5. Loss of heterozygosity (LOH) – mitotic recombination in which WT allele is lost
      1. Start: chromosome with mutation, mitotic recombination 🡪 should retain heterozygosity but one goes to fully mutated or no mutation at all.. hence loss of heterozygosity (ex. Rb – Retinoblastoma)

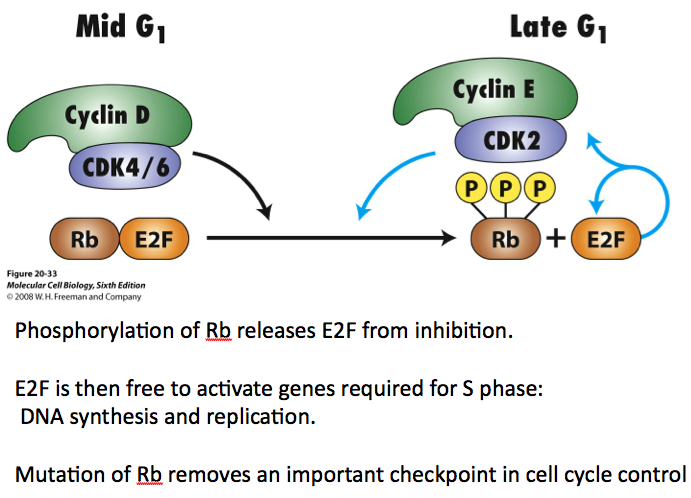
NOTES-------

Tumor Progression:

Genetically altered cell 🡪 Hyperplasia 🡪 Dysplasia 🡪 in situ cancer 🡪 Invasive cancer (w/ angiogenesis)

Ras Oncogene

* First oncogene discovered
* Encodes GTP-bp (G protein) which serve as on/off switch which activate/inactivate downstream molecules when bound to GTP but terminate effect when bound GTP is cleaved to GDP by intrinsic GTPase (ACT. ONCOGENE - TURNS RAS TO ALWAYS ON)
* 



p53 – in cancers, with damaged DNA, it can be phosphorylated and stabilized, stopping it from completing its normal function 🡪 stopping cell cycle or apoptosis

p53 mutations allow cancer cells to proliferate, oncogenic stress due to strong proliferation signals (Myc overexpression) 🡪 can cause apoptosis in p53 WT cells.

Li Fraumeni – multiple cancers, Autosomal dominant

Breast Cancer – small amount occurs b/c of inherited predisposition, mainly sporadic

* BRCA1 – encodes a protein which is involved in response to DNA damage and is phosphorylated by ATM protein
  + Interacts with Rad51 DNA repair
  + Her2/neu/c-ERBB2 receptor tyrosine kinase oncogene frequently amplified
  + DRUG – **HERCEPTIN** – targets her2/neu protein and inhibits growth
  + Ras, c-myc – mutations p53 and RB1 are lost in breast cancers
* Breast Cancers – Estrogen Receptor+ or ER-
* ER+ 🡪 depend on ER for growth
  + Anti-estrogens (tamoxifen) inhibit growth of ER+ tumors, but generally gain drug resistance

Prostate Cancer

* Growth dependent on androgen receptor (AR)
* Inhibition of testosterone synthesis (ligand for AR) blocks PC growth but tumors can become androgen independent